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Zinc: An Essential Trace Element with Potential Benefits to Soldiers*

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Zinc is a trace element known to be an essential nutrient for life. It functions as a cofactor for numerous enzymes, including those involved in DNA and RNA replication and protein synthesis. Soldiers represent a unique population faced with intense metabolic and mental demands, as well as exposure to various immune challenges. Some of these factors may affect their dietary zinc requirements. Although severe zinc deficiency is unlikely to occur, some soldiers may experience less than optimal zinc status because of diminished intake coupled with increased requirements. For those soldiers, supplemental dietary zinc may serve a protective function in numerous disease states affecting modern warfighters. This review highlights the importance of adequate zinc nutriture to soldiers and discusses the potential benefits of supplemental zinc in a number of diseases currently affecting soldiers, including diarrhea, respiratory diseases, malaria, and leishmaniasis.

Introduction

Zinc, a nutritionally essential trace element, functions as a cofactor for numerous enzymes, including those involved in DNA and RNA replication and protein synthesis. In 1963, the initial discovery of severe nutritional zinc deficiency in humans occurred in the Middle East.[1] Patients presented with symptoms that included growth retardation, anemia, hypogonadism, hepatosplenomegaly, rough dry skin, and mental lethargy. These symptoms were alleviated with iron supplements that are now thought to have contained zinc. In recent years, it has been suggested that zinc deficiency may not be limited to the severe form described in underdeveloped nations but may also occur in a mild form in developed nations.[2]

Mild deficiencies in zinc may not be diagnosed clinically because of the lack of reliable zinc status indicators and overt symptoms of deficiency. Serum and plasma zinc levels are most commonly used to assess zinc status but are affected by a number of factors, including infection, stress, exercise, and eating patterns.[3] In many cases, zinc deficiency is recognized when zinc supplementation provides measurable benefits. Examples include increased growth of zinc-supplemented children from middle to upper socioeconomic classes in the United States and Canada[4,5] and significantly greater birth weights and head circumferences of U.S. infants born to zinc-supplemented women.[6]

Soldiers represent a unique population faced with intense metabolic and mental demands as well as exposure to various immune challenges, particularly when operationally deployed or undergoing field training. Some of these stressors may affect the optimal dietary zinc requirement. Intense physical activity has been associated with diminished markers of zinc status in soldiers.[7-9] Singh et al.[8] reported reduced fasting plasma zinc concentrations among U.S. Navy Sea, Air, and Land trainees undergoing a 5-day training course, despite adequate zinc intake. In another study, U.S. Army soldiers participating in a 34-day field exercise had significantly decreased fasting plasma zinc concentrations and significantly increased urinary zinc output, compared with inactive soldiers.[9] Even moderate zinc deficiency can affect host defense systems, resulting in increased rates of opportunistic infections and death.[10,11] Although not tested among soldiers, supplemental zinc has been shown to reduce the incidence, severity, and duration of diarrhea[12] and the incidence of acute lower respiratory tract infections[13] in humans, disorders that have hindered warfighters throughout history. It is the objective of the present review to highlight the importance of adequate zinc nutriture for soldiers and to discuss the possible benefits of supplemental zinc for the prevention and treatment of these conditions and other pathophysiological conditions experienced by warfighters.

Diarrhea

Diarrhea has been a major cause of morbidity, hospitalization, and loss of duty days among military personnel for centuries.[14] In fact, diarrheal illness is the most common medical problem for U.S. troops during operational deployment.[15] Soldiers are especially prone to diarrhea because of travel, consumption of locally procured foods (including raw vegetables and poorly cooked meat products), and the use of nonpotable water or ice.[15] High rates of occurrence continue to be reported for soldiers deployed in recent conflicts. Outbreaks of diarrhea were reported for U.S. troops stationed in Beirut in the 1980s[16] and in the Persian Gulf during Operation Desert Shield and Operation Desert Storm.[17] Furthermore, high morbidity rates resulting from enteric diseases have been reported in Afghanistan and Iraq; up to 53 to 69% of Soviet troops had major gastrointestinal infections during the Afghan war,[18] and up to 69% of British troops and 36% of Australian troops reported diarrhea in Iraq during Operation Safe Haven (1991).[19]

Major causes of diarrhea among soldiers include *Shigella*,[20,21] *Campylobacter*,[22] and *Escherichia coli*.[20-22] Although the effects of zinc supplementation on morbidity attributable to these pathogens have not been adequately studied in soldiers, supplemental zinc has been shown to be of benefit for immune function in two studies of pediatric patients with shigellosis.[23,24] In a randomized, double-blind, placebo-controlled trial, children infected with *Shigella* were given standard antibiotic therapy as well as supplementation with either zinc (20 mg of ele-

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mental zinc, as zinc acetate, with a multivitamin for 14 days) or a multivitamin alone. Among the infected children treated with zinc and the multivitamin, the lymphocyte proliferation response increased ($p < 0.05$), compared with the control group given the multivitamin alone. Furthermore, levels of the *Shigella*-induced, antigen-specific antibody, Ipa-specific IgG, were higher ($p < 0.05$) at day 30 in the group receiving zinc supplementation.[23] In another study investigating the effect of zinc supplementation on shigellosis among children, Alam et al.[24] found that supplementation with zinc (15 mg/kg body weight per day for 30 days, in vitamin B syrup) in conjunction with standard antibiotic therapy resulted in improved ($p < 0.05$) intestinal permeability and coefficients of nitrogen absorption, compared with children fed vitamin B syrup alone.

Intake of food that is both safe and nutritious is paramount to the prevention and treatment of diarrhea. Maintaining zinc nutriture among soldiers may be especially important, because zinc deficiency is associated with increased risk of diarrhea, and diarrhea is associated with excessive zinc loss.[25-28] Zinc is essential for gut health, because it enhances the regeneration of gut epithelium, dictates the expression of some brush-border enzymes, and has profound effects on the gut mucosal immune system.[25,29] The importance of maintaining adequate zinc levels for protection against diarrhea is supported by the ability of zinc supplementation to protect against diarrhea-associated morbidity and death. In a recent review, Black[30] reported that, of the seven published trials on the effects of zinc supplementation on acute diarrhea among children, all of them reported shorter episode duration in zinc-supplemented groups, compared with placebo-treated control groups. Four of these trials were statistically significant ($p < 0.05$). In a meta-analysis of the five published trials investigating the effects of zinc supplementation on persistent diarrhea (>14 days), there was an overall 42% reduction ($p < 0.05$) in the rate of treatment failure or death among zinc-supplemented individuals.[30]

Respiratory Diseases

Respiratory diseases, including pneumonia, are leading causes of outpatient illness and infectious disease hospitalizations among soldiers.[31] Soldiers are at high risk for pneumonia and other respiratory diseases because of crowding and various immune challenges. During the Vietnam conflict, respiratory diseases were a leading cause of hospitalization or assignment to quarters among U.S. troops.[32] In more recent years, pneumonia outbreaks have been reported for U.S. military personnel stateside[33] and for troops deployed to the Middle East, including Iraq.[34,35] The pathogens responsible for pneumonia infections include *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, and there is currently little to no use of vaccines to prevent infection from either pathogen among military personnel.[31] Coupled with the lack of vaccines, the emergence of multidrug-resistant strains of pneumonia promises to present a formidable challenge to modern warfighters.

The effect of zinc supplementation on morbidity associated with pneumonia and other respiratory diseases has also been tested in humans. In a recent double-blind, placebo-controlled, trial among children, supplementation with zinc (20 mg/day, as zinc acetate, until the patient was released from the hospital) resulted in reduced ($p < 0.05$) duration of severe pneumonia, reduced duration of chest indrawing, diminished frequency of respiratory rates of >50 breaths per minute, lower rates of hypoxia, and overall shorter hospital duration.[36] In fact, the mean reduction of pneumonia-associated morbidity attributable to zinc supplementation was equivalent to 1 hospital day per child. In another randomized, double-blind, placebo-controlled, clinical trial of the effect of supplementation with zinc among children with severe acute lower respiratory tract infections, recovery rates from very ill status and from fever were faster ($p < 0.05$) for boys treated with zinc (20 mg/day, as zinc acetate, for 5 days), compared with those treated with placebo.[37]

The potential ability of zinc supplementation to provide protection against pneumonia in humans has also been tested. In a recent randomized, placebo-controlled trial, zinc supplementation (10 mg/day for infants or 20 mg/day for older children, as zinc gluconate, for 4 months, with a single dose of vitamin A) resulted in a lower ($p < 0.05$) overall incidence of pneumonia, compared with the placebo-treated group.[38] Taken together, these studies highlight the importance of maintaining adequate zinc status for the prevention and treatment of pneumonia and other respiratory diseases.

Malaria

Malaria is a life-threatening, mosquito-transmitted disease endemic in the tropics and some temperate regions. It is the most prevalent and pernicious parasitic disease among humans, and recent estimates suggest that malaria accounts for 400 million illnesses and >1 million deaths annually worldwide.[39,40] Malaria is a disease that has hindered soldiers for centuries and continues to be a threat to modern warfighters. In fact, malaria has reemerged as a major health concern because of the lack of a clinically proven vaccine, antimalarial drug resistance, insecticide resistance, and increased travel to disease-endemic areas.[41]

There are four *Plasmodium* species responsible for malarial infection, including *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Erythrocytic forms of *P. falciparum* (the most lethal form of *Plasmodium*) were reported for U.S. and Korean troops serving in Vietnam, despite weekly prophylactic treatment with chloroquine and primaquine base.[42] More recently, there has been an increase in malarial incidence among U.S. troops, mainly attributable to infection with *P. vivax*, which is endemic in areas including Korea,[43] Afghanistan,[18,44] and Iraq.[45] In 2003, 84 cases of malaria were reported for soldiers in the U.S. Army, up 25% from 2002.[46]

The positive correlation between diminished zinc status and malarial parasitemia[47] demonstrates the potential importance of maintaining adequate zinc nutriture for protection against malarial infection. The role of zinc in protecting against malaria may lie in its ability to support the immune system.[48] Zinc is essential for the production of IgG, tumor necrosis factor-α, and interferon-γ, all of which are involved in the development of resistance to malaria.[10] Furthermore, zinc status may be affected by malarial infection, because serum zinc concentrations vary inversely with malaria parasitemia, and increased zinc utilization occurs before the rupture of infected erythrocytes.[39]

Supplemental zinc has been shown to reduce malaria-associated morbidity among children. In a placebo-controlled trial of

zinc supplementation in Gambia, supplementation with zinc (20 mg of elemental zinc, as zinc gluconate, twice weekly for 15 months) resulted in a 32% reduction ($p < 0.10$) in health center visits attributable to *P. falciparum*.[49] A more recent placebo-controlled trial further demonstrated the ability of supplemental zinc to protect against malaria; children in Papua, New Guinea, who consumed supplemental zinc (10 mg of elemental zinc, as zinc gluconate, 6 days/week for 46 weeks) had 38% fewer ($p < 0.05$) health center visits attributable to *P. falciparum*, compared with placebo-treated children.[50] In that study, supplemental zinc tended to prolong the time to the first or only episodes of malaria attributable to *P. falciparum* and also protected against the most severe episodes; cases with extreme parasitemia (>100,000 parasites per μL) were reduced by 69%.

Leishmaniasis

Leishmaniasis is an arthropod-transmitted parasitic disease that is a risk for soldiers deployed to areas of Asia, Africa, southern Europe, and the Middle East.[51] Leishmaniasis has been subcategorized into three forms, namely, visceral, cutaneous, and mucosal. Visceral leishmaniasis is the most dangerous form and results in a syndrome that may include hepatosplenomegaly, pancytopenia, hypoalbuminemia, and in some cases death.[51] Cutaneous leishmaniasis (CL) results in a broad range of skin disorders, including papules, nodules, ulcerative lesions, and atrophic scars.[51] If left untreated, CL can result in secondary bacterial infections or mucosal leishmaniasis, which results in chronic nasal symptoms, including naso-oropharyngeal destruction.[51]

CL is the most common form of the disease and is a serious threat to soldiers deployed to the Middle East. In fact, the majority of the worldwide cases of CL occur in Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, and Syria.[51] Although visceral leishmaniasis was reported for at least eight U.S. soldiers participating in Operation Desert Storm,[52] in 2003 there were 400 reports of leishmaniasis among members of the U.S. Armed Forces and all except one of those cases was diagnosed as CL.[53]

To date, there are no vaccines or prophylactic compounds designed to prevent CL. Once CL is diagnosed, there are two modalities for treatment, local and systemic. Local modalities include freezing,[54] electrotherapy,[55] and topically applied paromomycin[56] and are generally recommended when one lesion site is apparent. When multiple lesion sites occur, systemic treatment is recommended. Pentavalent antimony compounds, namely, sodium stibogluconate and meglumine antimonite, are the most commonly used systemic treatments for CL; however, these drugs are costly and have been associated with numerous side effects.[51]

A number of recent studies have suggested a possible role for zinc as an inexpensive but effective anti-CL agent. In an in vitro study designed to test the effectiveness of zinc sulfate against the major causative strains of CL, *Leishmania major* and *Leishmania tropica*, Najim et al.[57] demonstrated that zinc sulfate added to liquid medium effectively killed both strains in a dose-dependent manner and the 50% lethal dose for zinc sulfate was lower than that for pentavalent antimony. In the same study, the efficacy of orally administered zinc sulfate as both a treatment for and a prophylactic agent against CL was tested in vivo. Orally administered zinc sulfate was effective when used as a prophylactic agent in mice; administration of 200 mg/kg for 5 days before infection with CL resulted in a lower mean lesion score after 4 weeks, compared with sham-treated control animals. Furthermore, when orally administered zinc sulfate was used as a treatment, the mean lesion score for mice infected with CL was reduced in zinc sulfate-treated animals, compared with sham-treated control animals, in a dose-dependent manner.

The ability of zinc sulfate to help cure CL among humans has been clinically tested. When patients presenting with CL were treated intralesionally with zinc sulfate (2%), hypertonic sodium chloride (7%), and pentavalent antimony compound, cure rates were comparable after a 45-day follow-up period.[58] Of the total lesions in each treatment group, zinc sulfate cured 94.8% of them, followed by pentavalent antimony (88.6%) and sodium chloride (85%). Oral treatment with zinc sulfate was also highly effective. When zinc sulfate (2.5, 5, or 10 mg/kg daily) was administered to patients with CL, cure rates were high after a 45-day follow-up period, in a dose-dependent manner (83.9%, 93.1%, and 96.9%, respectively).[59]

Conclusions

Modern warfighters face unique challenges, including intense metabolic and mental demands and exposure to various immune challenges. Maintaining adequate nutrition is paramount in preparing soldiers for many of these challenges. Zinc is an essential trace element that may be of special interest in military nutrition. Although severe zinc deficiency among soldiers is unlikely, soldiers experiencing diminished zinc status during field deployments have been observed,[7] and the intense physical activity sustained by soldiers may result in increased zinc loss.[9] Although the benefits of zinc supplementation have not been tested in soldiers, evidence from animal and clinical trials suggest that maintaining adequate zinc levels may reduce the incidence of diarrhea, respiratory diseases, and malaria and that supplemental zinc may be an effective treatment for CL, a condition currently affecting U.S. troops in Iraq.[53]

The cost of adding zinc to diets fed to soldiers, such as the U.S. Army meal, ready-to-eat (MRE), would be minimal, compared with the possible health benefits. Of the essential trace elements, zinc is among the least toxic, and estimates of safe upper limits approach 100 mg/day, well above the Recommended Dietary Allowance levels of 10 to 15 mg/day.[60] Simply replacing items in the MRE that are low in available zinc, such as jelly, with items that are higher in available zinc, such as peanut butter, would result in little or no added cost. Furthermore, zinc supplements (25 mg, as zinc gluconate) are readily available to consumers, at a cost of less than $0.05 per capsule. Because of the overall health benefits of maintaining adequate zinc nutriture and the possibility of increased zinc losses among soldiers, we recommend that all soldiers be fed diets that achieve a minimum of 20 mg/day before and during deployment to active duty. In certain situations, such as deployment to areas where malaria, diarrhea, or respiratory diseases are endemic, zinc supplementation should be considered. Furthermore, evidence cited in this review suggests that zinc supplementation should be considered as a primary treatment option for CL.

The benefits of maintaining adequate zinc status among soldiers are probably not limited to the disease states discussed in this review. Roles for zinc have been described for other important issues facing soldiers, including wound healing,[61] cognitive function and behavior,[62-64] and protein translation.[65] Because of these important roles of zinc in maintaining health and fighting disease, maintaining adequate zinc levels and supplementing with zinc in some cases should be considered in the formulation of diets for modern warfighters.

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